IN THE DRAWINGS

The attached 15 sheets of drawings includes changes to Fig. 1A, 1B, 1C, 2A, 2B, 2C, 5, 6A, 6B, 6C, 9A, 9B, 9C, 9D, 13 and 14. These sheets, which include the figures mentioned above, replace the original sheets including Figs. 1, 2, 5, 6, 9, 13 and 14.

Attachment: (15) Replacement Sheets

REMARKS/ARGUMENTS

Claims 29-41 are active and track prior elected claims 1-8. Claims 9-28 have been withdrawn from consideration. The specification has been revised to remove active hyperlinks and to comply with the sequence rules. Replacement drawings are provided. No new matter is believed to have been added. Favorable consideration of this amendment and allowance of the case are respectfully requested.

Restriction/Election

The Applicants previously elected with traverse **Group I**, claims 1-8, directed to insect acetylcholinesterase and the sequence of **SEQ ID NO: 1**. The requirement has been made FINAL. The Applicants thank Examiner Nashed for kindly examining the sequences of SEQ ID NOS: 3, 5, 7, 57, 122 and 126 and vacating any restriction of these sequences. Some non-elected claims have been revised to depend from claims in the elected group. The Applicants respectfully request that the claims of the nonelected group(s) or other withdrawn subject matter which depend from or otherwise include all the limitations of an allowed elected claim, be rejoined upon an indication of allowability for the elected claim, see MPEP 821.04. Non-elected claims have been cancelled without prejudice to their appearance in a Divisional Application.

Sequence Rule Compliance

The application was indicated as lacking compliance with the Sequence Rules because the sequences in certain figures were not identified by reference to sequence identifiers (SEQ ID NOs). This issue is moot in view of the amendment of the specification and drawings to refer to the appropriate sequence identifiers.

Sequence Listing Statement

As required by 37 C.F.R. 1.821(f), the sequence information recorded in the computer-readable form (CRF) of the substitute Sequence Listing is identical to that in the paper copy of the substitute Sequence Listing; or if this substitute Sequence Listing is electronically-filed, then the sequences in the electronically filed Sequence Listing are identical to the sequences disclosed in this application. Pursuant to 37 C.F.R. 1.821(g) the Applicants state that no new matter has been introduced.

Drawings—Objection

The drawings were objected to as not complying with 37 C.F.R. §1.121. Replacement drawings are submitted herewith. Accordingly, this objection may now be withdrawn.

Objection—Specification

The specification was objected to as containing active embedded hypertext links. These links have been amended to inactivate them. Accordingly, this objection may now be withdrawn.

Objections—Claims

Claims 2-8 were objected to for various reasons. These objections are moot in view of the cancellation of these claims.

Rejection—35 U.S.C. §101

Claims 1, 2, 3, 5, and 7 were rejected under 35 U.S.C. 101, as being directed to non-statutory subject matter. This rejection is moot in view of the cancellation of these claims.

Rejection—35 U.S.C. §112, second paragraph

Claims 1, 2, 3, 5, and 7 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. This rejection is moot in view of the cancellation of these claims.

Rejection—35 U.S.C. §112, first paragraph

Claims 1-3, 5, and 7 were rejected under 35 U.S.C. 112, first paragraph, as lack adequate enablement. This rejection is moot in view of the cancellation of these claims. The Applicants thank the Examiner for acknowledging the enablement of sequences having 90% identity. The term "sequence similarity", which appears in the new claims, is defined on page 6 of the specification, last paragraph and on page 7, first paragraph. Moreover, a method for calculating sequence similarity percentage is provided, i.e., using the BLAST program under default parameters and with an inactivated filter. Based on what was known in the art at the time of invention in combination with this disclosure one of skill in the art would have been enabled to determine sequence similarity without undue experimentation.

Rejection—35 U.S.C. §112, first paragraph

Claims 1-3, 5, and 7 were rejected under 35 U.S.C. 112, first paragraph, as lack adequate written description. This rejection is moot in view of the cancellation of these claims. With regard to the new claims the Applicants note that the new claims are directed to sequences having at least 90% sequence identity or 95% sequence similarity with SEQ ID NO: 1. The specification discloses the amino acid sequence of AChE1 of *A. gambiae* (comprising SEQ ID NO: 1), *Cu. Pipiens* and *Ae. Aegypti* (see Fig. 1). The inventors have found that the catalytic domain of *Cu pipiens* AChE1 has 93% identify and 96% similarity to SEQ ID NO: 1 and that the catalytic domain of *Ae aegypti* AChE1 has 92% identity and 97% similarity to SEQ ID NO: 1. As disclosed in the specification, page 1, lines 12-13, an

acetylcholinesterase belonging to the class E.C. 3.1.1.7 is an enzyme which hydrolyzes acetylcholine. Therefore, it is considered that one skilled in the art at the time of invention would have been enabled to identify a protein meeting the structural limitations of the new claims and determine whether the protein had acetylcholinesterase activity without undue experimentation based on methods well-known in the art at the time of invention, such as those disclosed by Kramer, et al., *Colorimetric Determination of Acetylcholinesterase Activity*, Anal. Chem. 30:251-254 (1958, attached). Accordingly, this rejection would not apply to the new claims.

Rejection—35 U.S.C. §102(a)

Claims 1, 2, 3, 5, and 7 were rejected under 35 U.S.C. 102(a) as being anticipated by Weil, et al., Proc. R. Soc. Lond. 13(2002) 269, 2007-2016. This rejection is moot in view of the attached English translations of the priority documents, French Applications 02/07622 and 02/13799.

Rejections—35 U.S.C. §102/§103

Claims 1-3, 5, and 7 were rejected under 35 U.S.C. 102(b) as being anticipated by either Bourguet, et al., J. Neurochemistry 67:2115 or Bourguet, et al., Biochem. Genetics 34:351, or as being obvious over either one of these two documents under 35 U.S.C. 103(a). adequate enablement. These rejections are moot since the prior claims have been cancelled. They would not apply to the new claims, because neither of these references disclose an isolated and purified polypeptide comprising SEQ ID NO 1 or a sequence exhibiting at least 90% identity or 95% similarity with the sequence SEQ ID NO 1, or such a sequence which is an insect AChE1 having a catalytic region comprising this sequence. Thus, this rejection would not apply to the new claims.

Rejections—35 U.S.C. §103

Claims 1-3, 5, and 7 were rejected under 35 U.S.C. 103(a) as being unpatentable over either Bourguet, et al., J. Neurochemistry 67:2115 or Bourguet, et al., Biochem. These rejections are moot since the prior claims have been cancelled. As noted above in response to the anticipation rejection, neither of these references teaches an isolated or purified polypeptide having the structural features required by the present claims. Thus, the references do not teach all the elements of the invention and cannot render it obvious.

Furthermore, Bourguet "A" (J. Neurochemistry, 1996, 67, 2115-2123) is a study on the characterization of 2 different acetylcholinesterase activities, named AChE1 and AChE2, in *Culex pipiens*. The authors attribute the AChE1 activity to a *hypothetical protein* in the form of a dimer (see page 2118, right col., 2nd §), but were unsuccessful to reduce the dimer into monomers (see page 2119, left col. 3rd §). The authors found that in the insecticide-sensitive strain S-LAB, the AChE1 activity is inhibited by 5×10^{-4} M propoxur (propoxur is a carbamate insecticide), whereas AChE2 activity is not inhibited, and in the insecticide-resistant strain MSE, AChE1 and AChE2 activities are not inhibited by 5×10^{-4} M propoxur. They also found that the AChE1 activity was more sensitive to malaoxon (an insecticide) than AChE2 activity, but both activities were similarly inhibited by the insecticides paraoxon and aldicarb. Hence, the authors theorized that the AChE1 activity was responsible for propoxur resistance. In addition, the authors theorized but did not show that the presence of two acetylcholinesterase activities in *Culex pipiens*, was related to 2 enzymes encoded by 2 different genes; these 2 enzymes not resulting from different posttranslational modifications of a single transcript, even if posttranslational modifications cannot be ruled out. Thus, it is clear that this document could not have enabled, suggested nor provided a reasonable expectation of success for the invention as now claimed.

The article of Bourguet "B" (Biochemical Genetics, 1996, 34, 351-362) was a study on two insecticide-resistant mosquito strains from the Caribbean. The authors found that these two strains possess two AChE1 activities: one AChE1 activity similar to that found in S-LAB (see above) strain and one AChE1 activity similar to that of MSE strain (see above). The authors attributed the AChE1 activities to a *hypothetical protein* in the form of a dimer (see Fig. 1, page 355) but do not disclose a method for separating the AChE1 enzyme responsible for sensitivity to insecticide from the one responsible for resistance to insecticide of the mosquito strains from the Caribbean, nor disclose how to reduce the dimer into monomers. Further, the authors did not show that it exists in these strains two *Ace.1* loci, encoding respectively an insecticide resistant (R) and a sensitive (S) AChE1 enzyme. Finally, the authors point out that *Ace.1* probes were not available to carry out studies based on DNA sequence and restriction profile comparisons (see the last § of the Discussion part).

Neither of the references above enabled the isolation or purification of a polypeptide having the structural and/or functional features of the invention. This is apparent from the review of these references above and also from the attached Declaration of M. Philippe FORT. Bourguet "A" and Bourguet "B" have shown two acetylcholinesterase activities in *Culex pipiens* but were unable to isolate and purified the proteins responsible for these two acetylcholinesterase activities. In view of the Declaration of M. Philippe FORT, it is important to note that Bourguet "A" and Bourguet "B" disclose functional acetylcholinesterase *activities* but not isolated or purified acetylcholinesterase enzymes.

In contrast to the prior art, the inventors have identified the *ace* gene responsible for resistance to organophosphorous compounds and/or carbamates, which is useful for screening novel insecticides and for the genetic detection of resistance to organophosphorus compounds and/or to carbamates in mosquito populations. The inventors have identified a new locus of the *ace* gene in the genome of *Anopheles gambiae* (see Example 2) and of 15 different

species of mosquitoes (see Example 4). They have shown that this new locus is involved in insecticide resistance in mosquitoes. The inventors have further shown that the insecticide resistance, at least in the mosquito *Culex pipiens* et *Anopheles gambiae*, is due to a single mutation in the amino acid sequence encoded by this new gene (substitution of the glycine located at position 119 to serine; G119S) (see Example 10). Bourguet "A" and "B" do not clearly show the nature of the acetylcholinesterase (AChE) involved in insecticide resistance and consequently could not have provided a reasonable expectation of success for the invention, nor could they have enabled the invention or suggested the specific structural characteristics of the claimed products.

Further, Bourguet "A" and "B" do not clearly show that two different acetylcholinesterase genes exist in insects since different tissue-specific posttranscriptional modifications of alternative splicing of a single *ace* gene cannot be ruled out. Bourguet "A" and "B" have only proposed hypotheses to explain the origin of two protein complexes extracted from *Culex pipiens*, which have different acetylcholinesterase activities differentially inhibited by carbamates. However, they have not provided any element which could lead one skilled in the art to identify the *ace1* gene.

On the other hand, the Inventors have clearly identified in *Anopheles gambiae* and *Culex pipiens* the presence of two distinct genes encoding AChE1 and AChE2 enzymes. The inventors unambiguously identify the *ace1* gene in insects (*Anopheles gambiae* and *Culex pipiens*) and clearly shown, at least in mosquitoes, that this gene is responsible for insecticide resistance. Indeed, this resistance in linked to a unique mutation in the AChE1 sequence encoded by the *ace1* gene, located in the region of the catalytic site of the enzyme.

Consequently, these rejections would not apply to the new claims because the prior art does not disclose or enable all the elements of the invention, namely isolated and purified polypeptides having the structures described in the claims, nor does it provide a reasonable

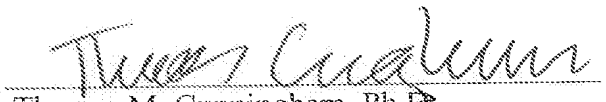
expectation of success for obtaining such polypeptides having these particular structures and properties.

Conclusion

This application presents allowable subject matter and the Examiner is respectfully requested to pass it to issue. The Examiner is kindly invited to contact the undersigned should a further discussion of the issues or claims be helpful.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, L.L.P.



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